Atorvastatin Does Not Affect the Antiplatelet Potency of Clopidogrel When It Is Administered Concomitantly for 5 Weeks in Patients With Acute Coronary Syndromes

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Background—The antiplatelet effect of clopidogrel may be attenuated by short-term coadministration of lipophilic statins. We investigated whether the coadministration of atorvastatin for 5 weeks in patients with acute coronary syndromes (ACS) could affect the antiplatelet potency of clopidogrel.

Methods and Results—Forty-five hypercholesterolemic patients with the first episode of an ACS were included in the study. Patients were randomized to receive daily either 10 mg of atorvastatin (n=21) or 40 mg of pravastatin (n=24). Thirty patients who underwent percutaneous coronary intervention (PCI) received a loading dose of 375 mg of clopidogrel, followed by 75 mg/d for at least 3 months. In the remaining 15 patients who refused to undergo PCI, clopidogrel therapy was not administered. Eight normolipidemic patients with the first episode of an ACS were also included and received only clopidogrel. The serum levels of soluble CD40L and the adenosine 5'-diphosphate– or thrombin receptor activating peptide-14–induced platelet aggregation, as well as P-selectin and CD40L surface expression, were studied at baseline (within 30 minutes after admission) and 5 weeks later. Neither atorvastatin nor pravastatin significantly influenced the clopidogrel-induced inhibition of platelet activation, nor did clopidogrel influence the therapeutic efficacy of atorvastatin.

Conclusions—Atorvastatin does not affect the antiplatelet potency of clopidogrel when coadministered for 5 weeks in ACS patients. (Circulation. 2004;109:1335-1338.)

Key Words: acute coronary syndromes • clopidogrel • platelets • drugs

Clopidogrel is an orally administered inactive thienopyridine prodrug that is metabolized primarily in the liver and converted into an active metabolite that selectively and irreversibly inhibits adenosine 5'-diphosphate (ADP)–induced platelet aggregation.1 Recently, it was shown that cytochrome P-450, isoenzyme 3A4 (CYP3A4), is primarily responsible for the metabolism and activation of clopidogrel in vivo.2 Several studies have shown that clopidogrel decreases the incidence of coronary artery stent thrombosis and is approved for reduction of myocardial infarction, stroke, and vascular death in patients with atherosclerotic vascular disease.3

Patients with symptomatic coronary artery disease and hypercholesterolemia are frequently given clopidogrel in conjunction with the HMG-CoA inhibitors (statins). Some of the statins (atorvastatin, lovastatin, simvastatin, etc) are metabolized in vivo predominantly by CYP3A4, whereas others are either not metabolized through cytochrome P-450 (pravastatin) or are metabolized through the isoenzyme 2C9 of cytochrome P-450 (fluvasatin).4 The possible interference of statins, metabolized through CYP3A4, with the antiplatelet efficacy of clopidogrel in vivo during the first days of their coadministration was recently addressed in patients undergoing elective coronary artery stent implantation. These studies provided controversial results suggesting that these statins either attenuate5 or do not influence6 the antiplatelet effect of clopidogrel.

In the present study, we investigated the consequences of concomitant use of atorvastatin and clopidogrel for 5 weeks in patients with the first episode of acute coronary syndrome (ACS) on the antiplatelet efficacy of clopidogrel. We show for the first time that the therapeutic efficacy of clopidogrel is not significantly affected by atorvastatin when both drugs are coadministered for 5 weeks in patients with ACS.

Methods

Patient Selection
Forty-five patients (mean age, 60.9±11.2 years; range, 49 to 72 years; 41 men, 4 women; body mass index, 28.2±3.5 kg/m²) with the first episode of an ACS (chest pain plus ECG changes and/or
increased biochemical markers) and LDL cholesterol levels $>$100 mg/dL (measured within 24 hours from the onset of symptoms) were included in the study. No patient had a previous history of cardiovascular disease, and none were taking medication before the coronary event. On admission, all patients received regular aspirin therapy (100 mg/d). Patients were randomized to receive daily either atorvastatin 10 mg (n = 21) or pravastatin 40 mg (n = 24) within 24 hours of admission. In 30 patients who underwent percutaneous coronary intervention (PCI) with stent implantation, clopidogrel therapy was initiated with a loading dose of 375 mg 6 to 12 hours before PCI, followed by 75 mg/d. In 15 patients who were treated with either atorvastatin (n = 8) or pravastatin (n = 7) and refused to undergo PCI, clopidogrel therapy was not administered. Eight normolipidemic patients (LDL cholesterol levels measured within 24 hours from the onset of symptoms $<$100 mg/dL) with the first episode of an ACS were also included in the study. They underwent PCI with stent implantation and received clopidogrel but no statin therapy (clopidogrel group). Compliance with treatment and with diet was assessed as previously described.7 There was no significant change in patients’ body weight or smoking habits during the study period. The Ethics Committee of the University Hospital of Ioannina approved the study, and written informed consent was obtained from each patient.

**Laboratory Determinations**

Venous blood samples for platelet and lipid analysis were drawn at baseline (within 30 minutes after admission) and 5 days later. Platelet aggregation to ADP (2, 5, and 10 μmol/L) or to thrombin receptor activating peptide-14 (TRAP-14; 10 μmol/L) was determined in platelet-rich plasma as previously described.8 The degree of platelet activation was also evaluated by FACSscan flow cytometry (Becton-Dickinson), determining the surface expression of P-selectin (CD62p) and CD40L induced by ADP or TRAP-14 (50 μmol/L) for either agonist) by use of the monoclonal antibodies CD62p and CD154, respectively. Flow cytometry results are presented as the mean fluorescence intensity of the activated sample minus the mean fluorescence intensity of the unactivated sample as previously described.9 Platelet activation in vivo was also studied by measuring the plasma levels of soluble CD40L (sCD40L) with a commercially available ELISA kit (Bender Medsystems). Serum lipid levels and biochemical markers of liver and muscle function were determined with an automatic analyzer (Olympus AU560).

**Statistics**

All values are expressed as mean±SD. ANOVA was assessed for comparison of baseline parameters among the study groups. Changes in the measured parameters after drug therapy were evaluated with the Wilcoxon signed rank test. Differences in the changes observed among studied groups were compared by ANCOVA, taking into account the baseline values as a covariate. Categorical variables were compared by Fisher’s exact $\chi^2$ test. A value of $P$≤0.05 was considered significant.

**Results**

There were no differences in age, sex, body mass index, or cardiovascular risk factors (current smoking, hypertension, diabetes mellitus) among patient groups (data not shown). No patient was under treatment with other medications that might influence cytochrome P-450 metabolism or might have interfered with platelet function. As shown in Table 1, the baseline values of all platelet activation parameters were not different among all studied groups. Clopidogrel administration for 5 weeks significantly attenuated the platelet aggregatory response to 3 different concentrations of ADP ex vivo. Similarly, clopidogrel inhibited ADP-induced expression of P-selectin and CD40L. Coadministration of clopidogrel with either atorvastatin or pravastatin inhibited ADP-induced platelet activation to the same extent as that observed for clopidogrel alone (Table 1). The posttreatment values of all the above platelet activation markers were lower but not significantly different compared with the baseline values in patients receiving atorvastatin or pravastatin (data not shown).

Clopidogrel did not influence the platelet-aggregatory response to TRAP-14 or the TRAP-14–induced surface expression of P-selectin and CD40L, although the posttreatment values were lower than the baseline values (Table 1). Similar results were obtained in patients treated with clopidogrel and atorvastatin or pravastatin and in those treated only with statin. Finally, the posttreatment plasma levels of sCD40L, used as a marker of platelet activation in vivo, were lower but
not significantly different compared with the baseline values in all patient groups (Table 1).

The present study also demonstrates that the coadministration of clopidogrel with atorvastatin for 5 weeks did not influence the hypolipidemic effect of atorvastatin, and the same results were obtained in patients treated with clopidogrel and pravastatin (Table 2). Importantly, none of our patients exhibited increased serum levels of liver or muscle enzymes (more than 3 times the upper normal limits) (Table 2) or myositis during the study period. As expected, no difference between baseline and posttreatment values in all lipid parameters studied was observed in normolipidemic patients treated with clopidogrel alone (data not shown). Finally, it must be noted that no significant difference between baseline and posttreatment body mass index values was observed in any patient group.

### Discussion

The results of the present study demonstrate that the coadministration of atorvastatin with clopidogrel in patients with the first episode of an ACS for 5 weeks does not significantly influence the antiplatelet activity of clopidogrel. Recent studies provided controversial results as to whether short-term (1 to 8 days) therapy with clopidogrel in conjunction with lipophilic statins could attenuate the antiplatelet efficacy of clopidogrel.5,6 Data from a post hoc analysis of the Clopidogrel for Reducing Events During Observation (CREDO) trial showed that there is no adverse effect on the 28-day or 1-year composite clinical end points with clopidogrel and statin coadministration.8,9 Similarly, the results of the prospective Maximal Individual Therapy of Acute myocardial infarction PLUS (MITRA PLUS) registry demonstrated that there was no significant difference between atorvastatin therapy and other statin therapies over a follow-up period of 14 months in the clinical outcomes (mortality and stroke) of patients receiving clopidogrel therapy.10 In accordance with these studies, our results demonstrate for the first time that atorvastatin plus clopidogrel therapy for 5 weeks is as effective at the level of platelet function as that obtained with clopidogrel alone or the combination of clopidogrel plus the hydrophilic pravastatin.

Overall, on the basis of the results of all recent studies, including ours, we may suggest that although CYP3A4-metabolized statins may influence the antiplatelet effect of clopidogrel within the first days of coadministration, concomitant use of these drugs for a longer period of time (4 to 5 weeks or longer) does not have an adverse interaction in platelet function and does not affect the clinical outcome.

It is known that the degree of competitive inhibition between 2 substrates of CYP3A4 depends on their relative concentrations as well as on their relative affinity for the CYP3A4 binding site.12 Clopidogrel exhibits lower affinity for CYP3A4 than atorvastatin or its lactone metabolite, and on a daily basis, its plasma levels may be remarkably lower than those of atorvastatin. However, we should not exclude the possibility that clopidogrel could affect the CYP3A4-catalyzed conversion of atorvastatin to its inactive lactone form, thus influencing the effectiveness of this statin. Nevertheless, our results provide evidence that clopidogrel does not influence the hypolipidemic effect of atorvastatin, and most importantly, none of our patients exhibited an elevation of liver and muscle enzymes that could be observed in cases of competitive inhibition of atorvastatin metabolism, resulting in high plasma concentrations of this statin.13

A limitation of the present study could be that the baseline values of all platelet activation parameters may be elevated because of the acute coronary event.14,15 However, according to our results, the posttreatment values of platelet activation to TRAP-14, the activity of which is not influenced by clopidogrel, were lower but not significantly different compared with the baseline values. The same phenomenon was observed in patients treated with statins alone. Furthermore, the plasma levels of sCD40L (used as a marker of in vivo platelet activation) were lower but not significantly different compared with the baseline values in all patient groups. These lower posttreatment values of platelet activation parameters reflect the trend of these parameters to reach the normal values, a phenomenon that is observed within 6 months after the onset of the ACS.15 Consequently, the significant de-

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**TABLE 2. Lipidemic Profile and Serum Levels of Liver and Muscle Enzymes in ACS Patients Treated With Clopidogrel and Statins**

<table>
<thead>
<tr>
<th>Lipid Parameter</th>
<th>Baseline</th>
<th>After Treatment</th>
<th>Change, %</th>
<th>Baseline</th>
<th>After Treatment</th>
<th>Change, %</th>
<th>Baseline</th>
<th>After Treatment</th>
<th>Change, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC, mg/dL</td>
<td>223±56</td>
<td>163±55</td>
<td>−26.5±4.4</td>
<td>241±30</td>
<td>172±49*</td>
<td>−28.8±5.1</td>
<td>245±53</td>
<td>188±31*</td>
<td>−23.6±6.5</td>
</tr>
<tr>
<td>LDL-C, mg/dL</td>
<td>144±63</td>
<td>91±41†</td>
<td>−37.0±9.1</td>
<td>154±42</td>
<td>98±41†</td>
<td>−36.1±7.6</td>
<td>162±48</td>
<td>113±35†</td>
<td>−30.4±7.8</td>
</tr>
<tr>
<td>TG, mg/dL</td>
<td>154±68</td>
<td>139±57</td>
<td>−9.5±1.1</td>
<td>167±31</td>
<td>148±34</td>
<td>−10.5±0.8</td>
<td>176±34</td>
<td>167±59</td>
<td>−4.8±0.7</td>
</tr>
<tr>
<td>HDL-C, mg/dL</td>
<td>48.0±9.2</td>
<td>49.7±7.1</td>
<td>3.1±0.6</td>
<td>44.3±5.6</td>
<td>45.8±13.0</td>
<td>3.2±0.6</td>
<td>47.8±8.9</td>
<td>48.9±5.6</td>
<td>1.2±0.3</td>
</tr>
<tr>
<td>ALT, IU/L</td>
<td>334±34</td>
<td>307±33</td>
<td>−8.6±0.3</td>
<td>334±34</td>
<td>307±33</td>
<td>−5.6±3.6</td>
<td>334±34</td>
<td>307±33</td>
<td>−5.6±3.6</td>
</tr>
<tr>
<td>AST, IU/L</td>
<td>70±20</td>
<td>75±19</td>
<td>7.1±0.3</td>
<td>70±20</td>
<td>75±19</td>
<td>7.1±0.3</td>
<td>70±20</td>
<td>75±19</td>
<td>7.1±0.3</td>
</tr>
<tr>
<td>CK, IU/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

TC indicates total cholesterol; LDL-C, LDL cholesterol; TG, triglycerides; HDL-C, HDL cholesterol; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; and CK, creatine phosphokinase.

†P<0.005; ††P<0.01 vs baseline values.
crease in platelet activation observed in the present study could be attributed exclusively to clopidogrel.

In conclusion, our study shows for the first time that the therapeutic efficacy of clopidogrel in patients with ACS is not significantly influenced by the concomitant administration of atorvastatin for 5 weeks. Moreover, clopidogrel does not affect the therapeutic efficacy of atorvastatin.

References
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*Circulation*. 2004;109:1335-1338; originally published online March 15, 2004;
doi: 10.1161/01.CIR.0000124581.18191.15
*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/109/11/1335

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